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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/089,312	03/29/2002	Gregory Gregoriadis	G0365.0355/P355	7293

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EXAMINER	
NGUYEN, DAVE TRONG	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 08/16/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/089,312	GREGORIADIS ET AL.	
	Examiner	Art Unit	
	Dave T Nguyen	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *12 February 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *21-49* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21-49* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *29 March 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3/29/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Applicant's election of the required or proposed species in the response dated Feb 12, 2004 has been considered, and is found persuasive. The species restriction regarding the moieties indicated as Y, X^2, R^8, R^5, X^1 and R^6 has been withdrawn by the examiner. The species restriction has been withdrawn by the examiner because all of the zwitterionic phospholipids in claim 21 share the moiety $R^3COOCH_2CH(OCOR^4)CH_2OP(O)O-$ linked to an alkanediyl-containing moiety, and because a representative number of species having the shared moiety as exemplified by the of the as-filed specification come from the prior liposomal art.

Claims 21-49 have been added after the filing date of the as-filed specification in the preliminary amendment dated.

Claims 21-49 are pending.

The specification is objected because the specification does not contain a brief description of drawings.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 21-49 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

In the latest preliminary amendment, claims 21-49 have been added. According to all of the base claims, there is a provision which states that "in which 50% by mole of groups R^3 and R^4 has a value for f o 0 and which comprises a compound in which R^3 and R^4 are the same and have a value of f of 0". It appears that no written support exists in the as-filed specification for the "which comprises a compound in which R^3 and R^4 are the same and have a value of f of 0"" nor is it apparent as to what is exactly as to what is meant by "which comprises a compound". Thus, this is new matter. The examiner notes that the only relevant written support as to the limitation of "50%" is shown on pare 4, wherein applicant states that "preferably the proportion of groups R^3 and R^4 which are saturated in a mixture is at least 50%".

As to the base claims and claim dependent there from, *e.g.,* claims 22 and 40, the claims recites that R_5 is a bond. However, the as-filed specification only provides sufficient description of two species for such a bond, wherein the two are either a methylene group or $C1_{-4}$-alkanediyl (see page 4). Such description does not provide sufficient description as to what are exactly representative of the "bond". As such, one skilled in the art would not have recognized that

applicant has sufficient description of such cationic compound, wherein R_5 is simply recited generically as a "bond".

Claims 21-49, encompassing a oral DNA vaccine of any prophylactic DNA for the purpose of generating a prophylactically relevant effect in any animal, *e.g.,* reptiles, birds, mammals, amphibians, wherein an oral administration routeis employed, are rejected under 35 U.S.C. 112, first paragraph, because the specification is enabling only for claims limited to:

1/ An immunogenic composition comprising the elements as set forth in claim 1;

2/ A method of eliciting a mucosal response in a mammal comprising orally administering the composition of 1/.

The specification does not reasonably provide an enablement for claims directed to the subject matter being sought in the claims, which are drawn to a genera of oral DNA vaccines and oral vaccination methods wherein a prophylactic DNA is employed.

Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in In re Wands, 858 F.2d 731, 8USPQ2d 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The specification does not reasonably provide enablement for any other *in vivo* DNA oral vaccination within the context claiming generically a enormous number of species of antigen encoded DNA for use in an enormous number of possible animal subjected to the vaccination such as farm animals, reptiles, fishes, monkeys, pig, and humans. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The specification provides factual evidence demonstrating a mucosal response elicited against a hepatitis B surface antigen Blab/c mice. However, the specification fails to provide factual evidence demonstrating how one skilled in the art reasonably extrapolates from the data obtained from the working examples to the broad subject matter as claimed, *e.g.,* a genera of DNA oral vaccines and vaccination methods for use in any animal, wherein a vaccination or prophylactic effect is generated. A simple elicitation of a mucosal imunne response against one particular antigen is not the same as claiming a master vaccination method for use with any prophylactic DNA against any infectious disease in a genus of animals. Pachuk teaches that even in 2000, "DNA vaccine technology, however, is still in its infancy and much research needs to be done to improve the efficiency with which these vaccines work in humans" (abstract). With respect to mucosal immunization, Pachuk while recognized that mucosal response can be elicited in mice by a oral vaccine comprising DNA entrapped in a colloid particle, Pachuk teaches on page 192, column 1:

> While a great deal of research continues in the area of mucosal immunization, it is clear that much remains to be learned that administration of DNA through multiple sites may be necessary to achieve protective immunity.

Reyes-Sandoval teaches that while DNA vaccines have shown progresses in a number of animal models, wherein a typically non-oral administration is employed, such is not the same as showing a protective effect in an subject in the real world, let alone a more challenging issue of oral route used for a DNA vaccine. More specifically, Reyes-Sandoval teaches on page 229, column 1:

> The results of a phase 1 trial with a DNA vaccine to the HbsAg [similar to the hepatitis surface antigen employed in this instant application] tested in 7 adult healthy volunteers by gene gun delivery [which is routinely employed successfully in small animal models such as mice or rats] were disappointing, the vaccine did not induce a detectable antibody response.

As such, a reasonable skilled artisan would not have concluded on the guidance and data provided by the as-filed specification that oral DNA vaccines as claimed broadly in the presently pending claims are reasonably enabling for a broad class of DNA coding for a antigen for use in a genera of animals, nor would one be able to determine, without undue experimentation, as to which species of DNA would be suitable for use as a "oral DNA vaccine" within the context of the as-filed specification.

eachuene therapy methods using a non-immunogenic product which is encoded by a DNA employed in the gene therapy method as claimed, particularly since the application does not provide a sufficient guidance as to what are exactly the "non-immunogenic product" that would generate a "useful" effect from the gene therapy methods as claimed. Given that gene therapy remains unpredictable at the time the invention was made (Anderson, 1998, Verma, 1997), it is not apparent how one skilled in the art determines, without undue experimentation, as to which of the "non-immunogenic" encoded DNA are "useful" in the gene therapy method as claimed, particularly on the basis of applicant's disclosure.

Major considerations for any gene transfer or nucleic acid therapy protocol involve issues such as amount of DNA constructs to be administered, what amount is considered to be therapeutically effective for all of the claimed nucleic acid molecules, the route and time course of administration, the sites of administration, successful uptake of the claimed DNA at the target site, expression of the DNA at the target site in amounts of effecting the treatment in a treated subject (Anderson (Nature, Vol. 392, 25-30, April 1998). More specifically, Anderson teaches that results in one particular animal model have not always reflected what happens in another animal model (page 28, column 1, first paragraph), that gene therapy is a powerful new technology that still requires several years before it will make a noticeable impact on the treatment of disease, and that several major deficiencies still exist including poor delivery systems, both viral and non-viral, and poor gene expression after genes are delivered

(page 30, column 1, last paragraph). Anderson further teaches that the reason for the low efficiency of gene transfer and expression in human patients is that we still lack a basis understanding of how vectors should be constructed, what regulatory sequences are appropriated for which cell types. Verma *et al.* (Nature, Vol. 389, 18, pp. 239-242, September 1997) also states that "the Achilles heel of gene therapy is gene delivery", that "thus far, the problem has been an inability to deliver genes efficiently and to obtain sustained expression", that gene delivery methods using non-viral vectors "suffer from poor efficiency of delivery and transient expression of the gene", and that "although there are reagents that increase the efficiency of delivery, transient expression of the transgene is a conceptual hurdle that needs to be addresses" (page 239, column 3, first paragraph). Furthermore, Verma *et al.* indicate that factors including the nature of the diseases and/or disorders, the nature of a DNA and/or target tissue, and a delivery system and/or amounts of the DNA complexes employed in the delivery system that would generate a therapeutic effect *in vivo* must be considered for any gene therapy method to be successful (page 238, columns 1 and 2). Even in 2000, Li, Gene Therapy, 7, 31-34, 2000, states:

> The science of nonviral gene delivery is still in its infancy. Further improvement of the delivery system will continuously rely on a better understanding of the cellular and *in vivo* barriers in gene transfer (page 34).

On the basis of transient gene expression and the doubts expressed by the art of record, the specification does not provide sufficient guidance and/or

factual evidence demonstrating a reasonable correlation between the disclosure including its exemplified examples and the subject matter being sought in the claims. Thus, it is not apparent how one skilled in the art determines, without undue experimentation, which of the disclosed DNA pharmaceutical kits generate a therapeutic effect in any and/or all gene therapy methods, nor is it apparent as to how one skilled in the art reasonably extrapolates from the *in vitro* delivery of a probe as exemplified by the specification to any and/or all pharmaceutical products as recited in the presently pending claims, particularly given the unpredictability of gene therapy and/or the doubts expressed in the art of record. Furthermore, the specification contemplates that any synthetic antigen encoded by a DNA entrapped within a polymeric matrix, wherein the antigen only is required to exhibit an "essential", 25% or 50% identity to a naturally occurring peptide or protein fragment, when used in any *in vivo* delivery method in any animal, would provide a desired therapeutically relevant effect. However, it is not apparent as to how one skilled in the art identifies and/or determines, without any undue experimentation, as to which DNA coding for "essentially identical amino acid sequence" is effective for use in an *in vivo* nucleic acid therapy method as claimed. The problem of predicting protein structure from mere sequence data of a single amino acid or nucleic acid sequence and in turn utilizing predicted structural determinations to ascertain functional aspects of any nucleic acid sequence and finally what changes can be tolerated with respect thereto is complex and do not invariably follow empirical rules. Unpredictability is keyed on the fact that simple analysis of primary, secondary, tertiary, and quaternary

structure of a polypeptide is not well correlated with the ability of the encoded DNA product to its functional activity because the relationship between the amino acid sequence of a polypeptide and its tertiary and/or quaternary structure is not well understood and is not invariably predictable (see Ngo *et al.,* in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz *et al.,* (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495). In addition of the lack of reasonable correlation between a therapeutically relevant effect of a naturally occurring peptide or protein known in the prior art and that of a synthetic peptide as contemplated by the claimed invention, one skilled in the art must also has to overcome the unpredictability of *in vivo* nucleic acid delivery methods within the context of therapeutic applications, as expressed by the art of record. Furthermore and even with DNA immunization methods wherein traditional routes such as IM is employed, the state of the art exemplified in McCluskie *et al.* (Molecular Medicine, 5, pp. 287-300, 1999) teach that "the realization that results in mice often do not predict the situation in humans has also led to a large number of DNA vaccine studies in nun-human primates", that "IM injection of plasmid DNA vaccines, while highly immunogenic in mice...was found to be only relatively so in chimpanzees..., and especially not all in Aotus monkeys", and that "it is probably safe to say that any vaccine that works in a human will work in a mouse, but not necessarily vice versa" (page 296, column 2, second and third paragraphs). In addition, McCluskie *et al.* teach that "the generally absent responses with the noninjected routes were not unexpected, as the mucosal surfaces are protective barriers, physiologically designed to limit uptake of

bacteria, viruses, antigens" (page 296, column 1), and that "although non-human primate models are frequently used for development and testing of human vaccines, it is not clear how predictive they will be in the case of DNA vaccines where efficacy, by virtue of the requirement first to transfect cells and express the antigen, relies on many factors other than immunological responses to the antigen" (page 297, column 1).

As such, it is not apparent how a skilled artisan would reasonably extrapolate from applicant's specification and its guidance to a method of employing any DNA/lipid complex to generate a therapeutically relevant mucosal immunity in any animal intended for a real-world treatment. At best, the specification coupled with the state of the prior art of record only provides reasonable enablement for the claimed embodiments as indicated at page 2 of the this Office action.

Thus, the specification is not enabling under 35 U.S.C. 112, first paragraph, for any and/or therapeutic/prophylactic nucleic acid constructs within the context of treatment and/or prevention of any disease in any subject, particularly on the basis of applicant's disclosure and the reasons stated in the art of record.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. ' 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.
> The following is a quotation of 35 U.S.C. ' 103 which forms the basis for all

obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

The following prior art rejections are applicable to liposomal preparations referred to in the working examples, which liposomal preparations or compositions are encompassed by the formulas given in the presently pending claims. More specifically, the main thrust of applicant's claimed invention is that no working examples have been provided in the prior art referred as WO 98/10748, and that applicant has provided a real working example showing a successful induction of a mucosal immunity against an encoded antigen by using essentially the same method and liposomal components as disclosed the '748 document. Thus, applicant's oral vaccines comprising an antigen encoded

plasmid vector entrapped in liposomes are contemplated as being a novel feature of the invention. However, insofar as the claims are drawn to old compositions and/or methods for eliciting an immune response as disclosed in the prior art, the claims are not patentable, as evidenced by the following prior art rejection.

Claims 21-49 are rejected are rejected under 35 U.S.C. 102(b) as being anticipated by, or in the alternative, under 35 USC 103 as being unpatentable over Gregoriadis (WO 98/10748).

Gregoriadis teaches mainly a DNA vaccine comprising antigen encoded plasmid vector which is entrapped in liposomes, which are composed of a cationic compound and at least one zwitterionic phospholipid. A cationic component can be DC-CHOL (page 23) and DOTAP, and DOTAP is preferred. Also see claim 13, and Tables 3, 4, 5, 7 on pages 25, 26, 27 and 34. According to claim 12 and page 10, lines 3-5, the phospholipids are phosphatidyl ethanolamines in which the acyl groups are unsaturated, of which one of them, referred as DOPE (dioleoyloxy phosphatidyl ethanolamine) is disclosed in the working examples. IN addition to said phosphatidyl ethanolamines, phosphatidylcholines can also be used. One of them, "DSPC" (distearoyloxy phosphatidylcholine) has been employed to prepare one of the preferred vaccine liposomal composition. Among the preferred liposomal compositions, PC:DOPE:DOTAP (Tables 3, 4, 5, 7) and DSPC:DOPE:DOTAP (Table 7) wherein the molar ratio can be 1:0.5:0.25. Notwithstanding the fact that the

intended use of the claimed products is not given any patentable weight for patentability regardless whether or not the new of use of the same product is disclosed in the prior art, oral administration of the vaccine composition is clearly taught by Gregoriadis on pages 5 and13. Given that the DNA-liposome entrapment method discloses in Gregoriadis is identical to that of applicant (see pages 11-12, which teaches dehydration-rehydration procedure and microfluidization), that the entrapment of plasmid DNA within the liposomal carrier, as taught by Gregoriadis (page 7 and page 8) provides greater freedom and reduces aggregation and nuclease attacks, and that these enhanced activities were shown in Gregoriadis a variety of administration routes (working examples), one would have reasonably conclude that an oral administration of the DNA entrapped liposomes as taught in the cited prior art would provide the same results, *e.g.,* an enhance of an immune response against an expressed antigen in the gut or M cells. As such, the claimed methods, drawn to an oral vaccination, is anticipatory, or in the alternative, is prima facie obvious over the prior art.

To the extent that the claims embraces the making and use of one or two phospholipids derived from known phospholipids including the exemplified ones, wherein minor modifications such as the length of the carbon chain, the molar ratio, the number of carbon atoms, a specific cationic moiety or anion, such would have been obvious to one of ordinary skill in the art as a matter of design choice, particularly since Gregoriadis teaches on page 8-10 that there is a great degree of flexibility in choosing liposomal components or obvious variants in

order to make and use liposome which is capable of entrapping plasmid vectors as the result of the hydration/rehydration method.

Thus, the claims are anticipated, or in the alternative, are *prima facie* obvious.

Additionally, Bischoff (US 2002/0151070 A1) is cited to indicate that at the time of filing mixtures of zwitterionic lipids and cationic lipids can be employed as adjuvants and/or minor adaptations for use in the making of a cell delivery composition (par. 0059).

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner *Dave Nguyen* whose telephone number is **571-272-0731**.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *Amy Nelson*, may be reached at **571-272-0804.**

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center number, which is **703-872-9306.**

Any inquiry of a general nature or relating to the status of this application should be directed to the *Group receptionist* whose telephone number is **(703) 308-0196**.

Dave Nguyen
Primary Examiner
Art Unit: 1632

DAVE T. NGUYEN
PRIMARY EXAMINER